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International Research and Development Corporation

SPONSOR: Velsicol Chemical Corporation

COMPOUNDS: 2-Methoxy-3,6-Dichlorobenzoic Acid (Banvel D)
2-Methoxy-5-Hydroxy-3,6-Dichlorobenzoic Acid (LCS-691)

SUBJECT: Comparative Acute Oral Toxicity (LD_{50}) in Male Albino Rats.

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I. SYNOPSIS

The acute oral toxicity (LD_{50}) in the male albino rat for Banvel D was found to be 2740 (2010-3740) mg./kg.; and for LCS-691 was found to be > 4200 but < 4640 mg./kg.

II. COMPOUNDS

The test compounds were received from the Velsicol Chemical Corporation, Chicago, Illinois on May 11, 1966. These were identified as indicated below:

2-Methoxy-3,6-dichlorobenzoic acid (Banvel D); Assay 99.7%; RS-M3o: 81062.

LCS-691 (2-Methoxy-5-hydroxy-3,6-dichlorobenzoic acid.

III. METHOD

Male albino, Spartan Sprague Dawley rats, weighing from 127 to 148 grams were used. The rats were separated into groups of 5 rats each and housed in an air conditioned environment. Food and water were available ad libitum except for a period of approximately 14 hours prior to administration of the compounds during which time they were deprived of food only.

Banvel D was orally administered at dosage levels of 1470, 1780, 2150, 3160, 3830 or 4640 mg./kg. to 5 rats at each respective dosage level. LCS-691 was orally administered at dosage levels of 3830, 4200 or 4640 mg./kg. to 5 rats at each respective dosage level. A greater number of dosages of the latter compound could not be administered because of compound scarcity.

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All rats were observed for pharmacodynamic and/or toxic signs at 0-60 minutes, 60-150 minutes, 150-300 minutes, at 24 hours and once daily thereafter for 14 days. The dead were necropsied.

IV. RESULTS

A. SANVEL D:

Sanvel D produced partial eye closure, bradycardia, bradypnea, diarrhea, peripheral vasodilatation, hypoactivity, spasticity, ataxia, sedation, inhibited placing, pinna and corneal reflexes, and death. Signs were seen within 60 minutes after administration. Depression, sedation and hypoactivity persisted for as long as 4 to 5 days in surviving rats at the upper dosage levels. Rats which recovered appeared essentially normal at the end of the 14-day observation period. The degree, incidence and duration of the signs recorded above were dose-related in nature.

One rat died at the 1470 mg./kg. dosage level within 2 hours after dosing; one died at 2150 mg./kg., also within 2 hours after dosing; 3 rats at each of the 3160 and 3830 mg./kg. dosage levels, and all 5 rats at the 4640 mg./kg. dosage levels died within 24 hours.

Necropsy of the dead revealed that compound related changes were limited to pulmonary congestion.

B. LCS-691:

LCS-691 produced an inhibition in heart and respiratory rate, salivation, peripheral vasodilatation, hypoactivity, ataxia, spasticity, inhibited placing, pinna and corneal reflexes and death. Signs were dose related in degree and duration. At the 3830 mg./kg. dosage level, all rats appeared normal within 24 hours. At the 4200

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and 4640 mg./kg. dosage levels, one rat, and all 5 rats respectively, died within 24 hours. The survivors at the 4200 mg./kg. dosage level continued to exhibit signs through 24 hours, but appeared essentially normal thereafter.

Necropsy of the dead revealed pulmonary congestion. No other compound related lesions were observed.

c. LD_{50} DATA

The LD_{50} data for both compounds appear in Table 1.

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TABLE 1. Acute Oral Toxicity (LD_{50}) of Banvel D and LCS-691 in the Male Albino Rat.

Compound	Dosage Level	No. Died/No. Dosed Observation								Total	LD_{50} and Confidence Limits (mg./kg.)
		Hours			Days						
		1	3	5	1	2	3	4	5-14		
Banvel D	1470		1/5							1/5	
	1780									0/5	
	2150		1/5							1/5	2740
	3100				3/5					3/5	(2010-3740)
	3830		1/5		2/4					3/5	
	4640				5/5					5/5	
LCS-691	3830									0/5	
	4200				1/5					1/5	> 4200
	4640		1/5	2/4	2/2					5/5	(- - - -)

Statistical References:

1. Thompson, W. R., Bact. Rev., 11: 115-145, 1947.
2. Weil, C. S., Biometrics, 8: 249-263, 1952.
3. Braun, C. A., Statistical Tables for Estimation of Median Effective Doses, Miles Laboratories, 1961.